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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/092,390	03/06/2002	Xuanchuan (Sean) Yu	LEX-0317-USA	8450

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EXAMINER	
NICHOLS, CHRISTOPHER J	

ART UNIT	PAPER NUMBER
1647	6

DATE MAILED: 09/17/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application N .	Applicant(s)	
	10/092,390	YU ET AL.	
	Examin r	Art Unit	
	Christopher Nichols, Ph.D.	1647	

-- The MAILING DATE of this communication appears on the cover sheet with th correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 June 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-4* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 5 .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Status of Application, Amendments, and/or Claims

1. Claims 1-4 are under examination.

2. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Art Unit 1647, Examiner Christopher James Nichols.

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

3. Claims **1-4** are rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a specific, substantial and credible asserted utility or a well-established utility.

4. The claims are directed to isolated nucleic acid molecule comprising the nucleic acid sequence of SEQ ID NO: 1 or variants thereof. The specification discloses that the nucleic acid SEQ ID NO: 1 encodes the amino acids of SEQ ID NO: 2 and 4. The nucleic acid of SEQ ID

NO: 1 encodes a protein that bears similarity to epidermal growth factor (EGF) and notch proteins as well as other proteins. A class known in the art to be large and diverse and the Specification as filed does not teach that SEQ ID NO: 1 shares any significant homology or structural motifs with known EGF molecules {Prenzel *et al.* (2001) "The epidermal growth factor receptor family as a central element for cellular signal transduction and diversification." Endocrine-Related Cancer **8**: 11-31}. The specification discloses no data for any activity of SEQ ID NO: 1. There are no working examples.

5. There are no well-established utilities for newly discovered biological molecules. However, the specification contains several assertions of utilities. Each will be discussed in turn.

a. *The nucleic acid molecule SEQ ID NO: 1 encodes an epidermal growth factor polypeptide:* The specification's assertion that SEQ ID NO: 1 encodes a novel EGF is credible. However, the highest homology identified in the Examiner's sequence search was 100% to a novel nucleic acid sequence disclosed by Nagase *et al.* (2001) "Prediction of the coding sequences of unidentified human genes. The complete sequences of 100 new cDNA clones from brain which code for large proteins in vitro." DNA Res. **8**(2): 85-95 wherein said sequence was described as a novel human protein with no known function. In addition, Vinter-Jensen (1999) "Pharmacological effects of epidermal growth factor (EGF)." APMIS Suppl. **93**: 5-42 teaches that the EGF family itself is large and complex. Therefore, the specification's assertion that SEQ ID NO: 1 is a novel epidermal growth factor (EGF) is not a substantial assertion of utility, since significant further research would be required of the skilled artisan to determine what SEQ ID NO: 1's properties are. Nor is the Specification assertion of SEQ ID NO: 1's identity specific, as

Vinter-Jensen teaches the broad and diverse physiological effects of the EGF family members (pp. 6).

b. *The nucleic acid molecule SEQ ID NO: 1 encodes polypeptides (SEQ ID NO: 2 and SEQ ID NO: 4) with epidermal growth factor (EGF) biological activity:* The specification asserts that SEQ ID NO: 1 encodes a protein with epidermal growth factor activity based solely on its sequence similarity to prior art of EGF-like polypeptides that have been characterized. However, this assertion would not have been accepted by one skilled in the art because the art establishes that EGF-like proteins, while structurally similar, are functionally diverse {Grimmond *et al.* (15 November 2000) "Cloning, Mapping, and Expression Analysis of a Gene Encoding a Novel Mammalian EGF-Related Protein (*SCUBE1*)." Genomics **70**(1): 74-81}. Regarding the use of sequence homology to predict function, the problem of predicting protein structure from sequence data and in turn utilizing predicted structural determinations to ascertain functional aspects of the protein is extremely complex. While it is known that many amino acid substitutions are generally possible in any given protein the positions within the protein's sequence where such amino acid substitutions can be made with a reasonable expectation of success are limited. Certain positions in the sequence are critical to the protein's structure/function relationship, e.g. such as various sites or regions directly involved in binding, activity and in providing the correct three-dimensional spatial orientation of binding and active sites. These or other regions may also be critical determinants of antigenicity. These regions can tolerate only relatively conservative substitutions or no substitutions [see Wells (18 September 1990) "Additivity of Mutational Effects in

Proteins." Biochemistry **29**(37): 8509-8517; Ngo *et al.* (2 March 1995) "The Protein Folding Problem and Tertiary Structure Prediction, Chapter 14: Computational Complexity Protein Structure Prediction, and the Levinthal Paradox" pp. 492-495]. However, Applicant has provided little or no guidance beyond the mere presentation of sequence data to enable one of ordinary skill in the art to determine, without undue experimentation, the positions in the protein which are tolerant to change (e.g. such as by amino acid substitutions or deletions), and the nature and extent of changes that can be made in these positions. Although the specification outlines art-recognized procedures for producing and screening for active muteins, this is not adequate guidance as to the nature of active derivatives that may be constructed, but is merely an invitation to the artisan to use the current invention as a starting point for further experimentation. Even if an active or binding site were identified in the specification, they may not be sufficient, as the ordinary artisan would immediately recognize that an active or binding site must assume the proper three-dimensional configuration to be active, which conformation is dependent upon surrounding residues; therefore substitution of non-essential residues can often destroy activity. The art recognizes that function cannot be predicted from structure alone [Bork (2000) "Powers and Pitfalls in Sequence Analysis: The 70% Hurdle." Genome Research **10**:398-400; Skolnick and Fetrow (2000) "From gene to protein structure and function: novel applications of computational approaches in the genomic era." Trends in Biotech. **18**(1): 34-39, especially p. 36 at Box 2; Doerks *et al.*, (June 1998) "Protein annotation: detective work for function prediction." Trends in Genetics **14**(6): 248-250; Smith and Zhang (November 1997) "The challenges of genome sequence

annotation or 'The devil is in the details'." Nature Biotechnology **15**:1222-1223; Brenner (April 1999) "Errors in genome annotation." Trends in Genetics **15**(4): 132-133; Bork and Bairoch (October 1996) "Go hunting in sequence databases but watch out for the traps." Trends in Genetics **12**(10): 425-427]. Thus sequence homology is not a reliable basis upon which to establish biological activity. Furthermore, the art acknowledges that function cannot be predicted based solely on structural similarity to a protein found in the sequence databases. The art clearly shows that structural similarity in the epidermal growth factor family is not predictive of expression patterns or functional similarity. Therefore, the specification's assertion that SEQ ID NO: 1's endcoded polypeptides have EGF activity is not a substantial assertion of utility, since significant further research would be required of the skilled artisan to determine what those activities are.

c. *The nucleic acid molecule SEQ ID NO: 1 can be used as a probe or primer is assays such as hybridization assays, using oligonucleotides, addressable arrays, microarray-based analysis, nucleic acid probes, screening libraries, assessing gene expression patterns, RLFP analysis, PCR based screening methods, and microarrays:* The specification asserts that SEQ ID NO: 1 is useful as probes to detect genes or variants thereof, to identify potential genetic disorders, or to regulate expression of SEQ ID NO: 1. This asserted utility is credible, but is neither substantial nor specific. Since there is no substantial utility for the nucleic acid molecule, there is also no substantial utility for the probes to identify SEQ ID NO: 1 in tissues or biological samples. Also, no polymorphism or mutation of SEQ ID NO: 1, including polymorphism identified in the Specification at pp. 17, is associated with any known or characterized disease, disorder,

or condition. For instance Ito *et al.* (2002) "Notch3 gene polymorphism and ischaemic cerebrovascular disease." J Neurol Neurosurg Psychiatry **72**: 382-384 teaches five polymorphisms identified in the Notch3 coding sequence (Abstract). However, the existence of identified polymorphisms *inter alia* does not necessarily denote any clinical or scientific significance as noted by Ito *et al.* Thus it would take significant further research to determine if the instantly claimed novel ECF could be used as probes for particular diseases, since no nexus between a disease state and an alteration in SEQ ID NO: 1 expression levels or form (i.e., mutations) has been disclosed in the specification. Also, all nucleic acid molecule can be used as "probes" to detect the genes, thus the asserted utility is not specific.

d. *The nucleic acid molecule SEQ ID NO: 1 is useful to design antisense molecules and double stranded oligonucleotides:* Again, this asserted utility would only be substantial if the encoded polypeptide has a substantial utility. Otherwise, significant further research would be required of the skilled artisan to use the claimed nucleic acid molecules to make ribozymes and antisense molecules, since it is unclear when it would be desirable to use ribozymes.

e. *The nucleic acid molecule SEQ ID NO: 1 is useful to make a cDNA library:* Again, this asserted utility would only be substantial if the encoded polypeptide has a substantial utility. Otherwise, significant further research would be required of the skilled artisan to use the claimed nucleic acid molecules to make a cDNA library, since it is unclear when it would be desirable to use the cDNA library.

f. *The nucleic acid molecule SEQ ID NO: 1 can be used to make polypeptides (SEQ ID NO: 2 and 4) for analysis, characterization, or therapeutic uses:* This asserted utility is not substantial. In recombinately expressing a polypeptide, the polynucleotide is transfected into a host cell and then the protein is recovered. However, the instant specification does not disclose any known function for the claimed polypeptide or any disease state, toxin, or poison associated with SEQ ID NO: 1. In addition, this utility assertion is not specific as it can be applied to any given polynucleotide. Therefore, it is not clear how the skilled artisan would use a polypeptide manufactured by this method, for analysis, characterization, or therapeutic uses. Since significant further research would be required to determine how to use the identified polynucleotide, the asserted utility is not substantial.

g. *The nucleic acid molecule SEQ ID NO: 1 can be used to RNA for analysis, characterization, or therapeutic uses:* This asserted utility is not substantial. In recombinately expressing RNA, the polynucleotide is transfected into a host cell and then the RNA is recovered or the RNA is transcribed in a cell-free system. However, the instant specification does not disclose any known function for the claimed polypeptide or any disease state, toxin, or poison associated with SEQ ID NO: 1. In addition, this utility assertion is not specific as it can be applied to any given polynucleotide. Therefore, it is not clear how the skilled artisan would use a RNA manufactured by this method, for analysis, characterization, or therapeutic uses. Since significant further research would be required to determine how to use the identified polynucleotide, the asserted utility is not substantial.

h. *The nucleic acid molecule SEQ ID NO: 1 is useful for making transgenic animals:* No phenotype has been disclosed for such transgenic animals. In the absence of such disclosure, the skilled artisan would have to experiment significantly in order to determine how the transgenic animals could be used. Therefore, the asserted utility is not substantial.

i. *The nucleic acid molecule SEQ ID NO: 1 can be used to in computer based screening assays:* The specification asserts that SEQ ID NO: 1 is useful as probes to detect genes or variants thereof, to identify potential genetic disorders, or to regulate expression of SEQ ID NO: 1 in computer databases. This asserted utility is credible, but is neither substantial nor specific. Since there is no substantial utility for the nucleic acid molecule, there is also no substantial utility for the probes to identify SEQ ID NO: 1 in tissues or biological information stored in computer databases. It would take significant further research to determine if the instantly claimed novel EGF could be used as probes for particular diseases, since no nexus between a disease state and an alteration in SEQ ID NO: 1 expression levels or form (i.e., mutations) has been disclosed in the specification. Also, all nucleic acid molecule can be used as "probes" to detect the genes or sequences of interest in a BLAST-like search, thus the asserted utility is not specific.

j. *The nucleic acid molecule SEQ ID NO: 1 can be recorded on computer readable media:* This asserted utility is not substantial. The instant specification does not disclose any known disease state, toxin, or poison associated with SEQ ID NO: 1 or its activity. Therefore, it is not clear how the skilled artisan would use the computer readable media as identified by this method, for therapeutic or diagnostic uses. Since significant further

research would be required to determine how to use the identified nucleic acid or polypeptide, the asserted utility is not substantial.

k. *The nucleic acid molecule SEQ ID NO: 1 can be used in chromosome mapping:* In order to be useful as a chromosomal probe, the precise chromosomal map position must be disclosed. The specification discloses that SEQ ID NO: 1 is on human chromosome 5. Substantial further research would be required for the skilled artisan to determine where this particular sequence is mapped in order to use the nucleic acid molecule in the asserted utility as a chromosomal map probe. The asserted utility is also not specific, since the entire class of genes can be asserted to be used in this way.

l. *The nucleic acid molecule SEQ ID NO: 1 is useful for encoding antigenic portions of SEQ ID NO: 2 and 4:* This utility is also not substantial, because there is no substantial utility for the full-length polypeptide. If substantial further research is required to determine how to use the full-length polypeptide, then substantial further research is also required to determine how to use antibodies generated from antigenic fragments.

m. *The nucleic acid molecule SEQ ID NO: 1 can be used to make chimeric proteins:* This asserted utility is not substantial. The instant specification does not disclose any known disease state, toxin, or poison associated with SEQ ID NO: 1 or its activity. Therefore, it is not clear how the skilled artisan would use a chimeric polypeptide for therapeutic, diagnostic, or research uses. Since significant further research would be required to determine how to use the identified chimeric polypeptide, the asserted utility is not substantial.

n. *The nucleic acid molecule SEQ ID NO: 1 has therapeutic uses:* This asserted utility is also not substantial. The instant specification does not disclose any known disease state, toxin, or poison associated with SEQ ID NO: 1 or its activity. Therefore, it is not clear how the skilled artisan would use the polynucleotide, for therapeutic uses. Since significant further research would be required to determine how to use the identified polynucleotide, the asserted utility is not substantial.

6. Therefore, in the absence of a well-established utility, and the absence of a specific, substantial and credible asserted utility, the claimed invention lacks patentable utility under 35 U.S.C. § 101.

7. If Applicant can submit evidence (in the form of a declaration under 37 CFR 1.132 or post-filing date publications) supporting the specification's assertion that SEQ ID NO: 1, 2, or 4 has a specific function similar to a known epidermal growth factor or notch protein, wherein the specific function was predicted by the specification as originally filed, such would be viewed favorably as evidence of patentable utility.

8. Claims **1-4** are also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a credible, specific and substantial asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

9. Claims **1-4** are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The specification does not contain a written description of variants and fragments of the claimed peptide-transmitter-like receptor polypeptide.

10. *Vas-Cath Inc. v. Mahurkar*, 19USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See *Vas-Cath* at page 1116).

11. With the exception of **SEQ ID NO: 1**, the skilled artisan cannot envision the detailed chemical structure of the encompassed polypeptides, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The compound itself is required. See *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016.

12. One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481 at 1483. In *Fiddes*, claims directed to mammalian FGF's were found to be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence.

13. Therefore, only isolated polypeptides comprising the amino acid sequence set forth in SEQ ID NO: 1, but not the full breadth of the claim meets the written description provision of 35 U.S.C. §112, first paragraph. Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

14. Claim **2** is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

15. The term "stringency" in claim 2 is a relative term which renders the claim indefinite. The term "stringency" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. Neither the specification nor the art defines the term unambiguously. Thus the metes and bounds of the claims cannot be determined.

Summary

16. Claims 1-4 are hereby rejected.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Christopher Nichols, Ph.D.** whose telephone number is 703-305-3955. The examiner can normally be reached on Monday through Friday, 8:00AM to 5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, **Gary Kunz, Ph.D.** can be reached on 703-308-4623. The fax phone numbers for the organization where this application or proceeding is assigned are 703-872-9306 for regular communications and 703-872-9307 for After Final communications. The fax phone numbers for the customer service center is 703-872-9305.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Elizabeth C. Kemmerer

CJN
September 4th, 2003

ELIZABETH KEMMERER
PRIMARY EXAMINER